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ABSTRACTS OF PAPERS

Part 2

216th ACS National Meeting

0-8412-3627-5

American Chemical Society

Boston, MA

August 23-27, 1998

017. APPLICATION OF MASS SPECTROMETRY AND GEL ELECTROPHORESIS TOWARDS DRUG DISCOVERY: PROTEOMICS. Rachel R. Ogorzalek Loo and Philip C. Andrews, University of Michigan, Department of Biological Chemistry, Ann Arbor, MI 48109 and James D. Cavalcoli, Brian Moldover, and Ruth A.VanBogelen, Parke-Davis Pharmaceutical Research, Division of Warner-Lambert Company, 2800 Plymouth Road, Ann Arbor, MI 48105

Strides have been made in recent years to interface the high resolution separation power and capacity of polyacrylamide gel electrophoresis (PAGE) and the high sensitivity, speed, and mass measurement accuracy of mass spectrometry (MS) for protein analysis. Our method utilizes matrix-assisted laser desorption/ionization (MALDI) for the *direct* MS interrogation of the PAGE-separated proteins. A proteomics-based approach utilizing PAGE-MS has been developed to uncover new protein targets for drug discovery. Using *E. coli* as an example, bacterial proteins are isolated and separated by isoelectric focusing PAGE and directly analyzed by MALDI-MS. Hundreds of proteins have been mapped and identified. By changing the organism's growth conditions and environment, for example, in the presence of drugs, the mechanism of action and the affected biochemical pathways can be elucidated.

018. ARGININE VASOPRESSIN (AVP) ANTAGONISTS. PYRROLO [2,1-c][1,4] BENZODIAZEPINES. J. Donald Albright,*[a], M.F. Reich,[a] E. Delos Santos,[a] J.P. Dusza,[a] F.W. Sum,[a] A.M. Venkatesan,[a] J. Coupet,[a] P.S. Chan,[a] X. Ru,[a] H. Mazandarani,[a] and T. Bailey[b]. [a]Wyeth-Ayerst Research, Pearl River, N.Y. 10965;[b]Wyeth-Ayerst Research, Princeton, N.J. 08543-8000

Hyponatremia occurs in the syndrome of inappropriate antidiuretic hormone secretion (SIDH), in patients with congestive heart failure, liver cirrhosis with ascites, renal failure and other disorders where the plasma vasopressin concentrations are inappropriately high for any given plasma osmolality. A V_2 receptor antagonist acting at the V_2 receptors in the collecting ducts where vasopressin (AVP) acts to control water reabsorption would be the drug of choice versus a conventional diuretic in disease states characterized by hyponatremia. The design, synthesis and structure-activity relationships of derivatives of the tricyclic heterocycle pyrrolo [2,1-c][1,4]benzodiazepine will be discussed. These derivatives exhibit potent vasopressin antagonist versus rat and human V_1 and V_2 receptors. Differences in the antagonist activity between rat and human receptors are disclosed as well as substitution patterns which enhanced the selectivity for human V_2 receptors versus human V_1 receptors. The derivatives VPA-985 was chosen for its selective V_2 antagonist activity to undergo evaluation as a clinical candidate and is now in phase II clinical studies as a potent orally active aquaretic.

19. SYNTHESIS OF 1,1-DIOXO-2,4-DIPHENYL-1,2-DIHYDROBENZOTHIAZINES: DISCOVERY OF PD180988, A POTENT ET_A SELECTIVE ANTAGONIST

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cently in our laboratories, the weakly active endothelin antagonist, PD166114 (IC_{50}= 83nM) was prepared and closed. Further optimization of the substitutions on the pendant rings has led to the discovery of a potent ET_A lective antagonist, PD180988. This compound was found to be 180-fold more potent, possessing an IC_{50} binding finity at human cloned ET_A receptor of 0.46nM. PD180988 was also found to exhibit a strong functional inhibitory tivity against ET-1-induced vasoconstriction in the ET_A-specific rabbit femoral artery (Kb = 0.026nM). Binding finity at the ET_B receptor (IC_{50}= 2200nM) was over 4000-fold less than the corresponding ET_A value, which monstrated a high ET_A receptor selectivity. PD180988 was found to be rapidly absorbed in male Wistar rats and is highly bioavailable (60-75%) by oral route. Chemical synthesis, lead optimization and additional armacokinetic properties of PD180988 will be presented.